3,6-DICHLOROPICOLINIC ACID-2,6-^{14}C

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SUMMARY

A 20.4 mCi sample of 99% radiochemically pure 3,6-dichloropicolinic acid-2,6-^{14}C with a specific activity of 11.6 mCi/mmole was synthesized *via* a five step process from glutarimide-2,6-^{14}C.

Key words: 3,6-dichloropicolinic acid-2,6-^{14}C, 2,3,6-trichloropyridine-2,6-^{14}C, 3,6-dichloro-2-methylthiopyridine-2,6-^{14}C, 3,6-dichloro-2-methylsulfonylpyridine-2,6-^{14}C, 3,6-dichloropicolinonitrile-2,6-^{14}C.

INTRODUCTION

3,6-Dichloropicolinic acid is an active ingredient in the Dow herbicide sold under the trademark LONTREL*. A carbon-14 labeled sample was required for environmental studies.

DISCUSSION

3,6-Dichloropicolinic acid was synthesized *via* the five step sequence depicted in Scheme I. The process was initially developed using unlabeled reactants (pilot run).

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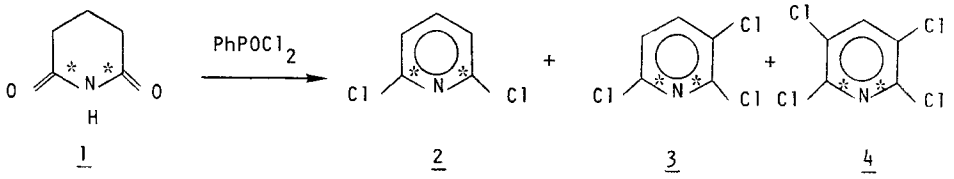
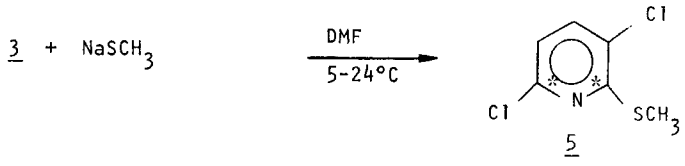
SCHEME I

Step 1



1 2 3 4

Step 2



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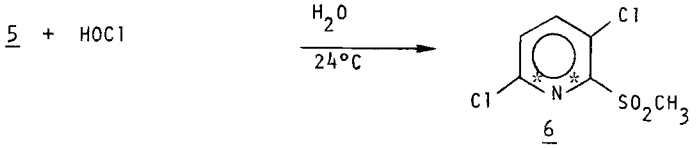
Step 3



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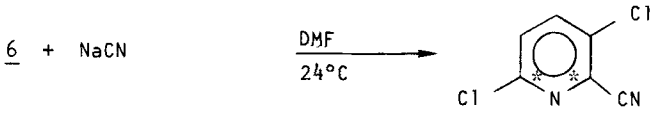
Step 4



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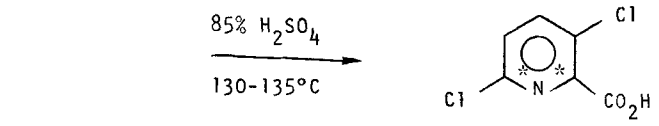
Step 5



The synthesis of glutarimide-2,6-^{14}C (Steps 1 and 2) has previously been reported (1).

There are currently several techniques available for converting glutarimide into 2,3,6-trichloropyridine (1-4). The process depicted in Step 1 represents a modification of that used for the synthesis of 2,3,5,6-tetrachloropyridine (4). The above reaction was conducted at 24°C for 16 hr to obtain maximum conversion to 3 and subsequently at 120°C for 1.0 hr to ensure complete reaction. In this manner the tracer synthesis afforded a 68.4% yield of chlorinated pyridines consisting of 3.7% 2, 47.9% 3 and 16.8% 4. The overall yield is somewhat lower than the 85% yield reported earlier (4) and may reflect the purity of the starting glutarimide-2,6-^{14}C used in the above sequence.

The thiomethylation (Step 2) proceeds very readily at or below room temperature affording 3-chloro-2,6-bis-methylthiopyridine (ca 5%) as the only major by-product.

In previous syntheses of 3,6-dichloropicolinic acid-2,6-^{14}C conducted in this laboratory, conversion of sulfide 5 to sulfone 6 was accomplished at 90°C using 30% hydrogen peroxide in glacial acetic acid. Unfortunately, the yields varied dramatically between 50% and 90% with the lower yields consistently being obtained in the tracer syntheses. Therefore a new oxidation procedure was sought, leading to that depicted in Step 3. This process consistently affords 85-95% yields in both the pilot and tracer syntheses. Furthermore, the

reaction is complete within two hours at room temperature representing much milder conditions than those for the peracetic acid process.

The conversion of sulfone 6 to the picolinonitrile 7 (Step 4) was accomplished in a 94% yield and subsequent hydrolysis (Step 5) afforded 3,6-dichloropicolinic acid-2,6-^{14}C in a 77% yield.

Using the above sequence, 20.4 mCi of 99% radiochemically pure 3,6-dichloropicolinic acid-2,6-^{14}C was isolated as a white crystalline solid.

EXPERIMENTAL

All GLC analyses were conducted on a Hewlett Packard 5830A instrument using a 2' x 4 mm glass column containing 10% OV 17 on 80/100 chromasorb WHP. The following conditions were used unless otherwise stated: Inj. Temp.: 250°C, FID Temp.: 300°C, Temperature Program: 100° to 250°C at 20°/min, Time at 100°C: 2.0 min, Time at 250°C: 5.0 min, N_2 flow: 60 ml/min. The following retention times were observed: 2, 2.99 min; 3, 4.25 min; 4, 5.09 min; 5, 5.58 min; 6, 8.59 min; 7, 5.51 min.

2,3,6-Trichloropyridine-2,6-^{14}C 3.

Glutarimide-2,6-^{14}C (333.4 mg, 2.948 mmole, 64.3 mCi at 21.8 mCi/mmole), phenylphosphonic dichloride (5 ml) and phosphorous pentachloride (2.46 g, 11.8 mmole) were added to a 100-ml round-bottomed flask equipped with a stirring bar, condenser, and $CaCl_2$ drying tower and the mixture stirred at 24°C for 16 hr and at 120°C for 1.0 hr. The solution was cooled in an ice bath, treated slowly with ice and neutralized with ca. 30 ml of 20% NaOH. The mixture was extracted continuously with 20 ml of n-pentane for 5.5 hr, the solvent removed in

vacuo and the isomeric chlorinated pyridines partially separated by preparative HPLC (Whatman 50 cm x 9.4 mm Magnum 9 Partisil 10 silica gel column, 4:1 (v/v) n-hexane:benzene). The separation was completed on a column containing 100 g of Brinkman silica gel G60 using 5:95 (v/v) EtOAc:n-hexane affording 0.1102 mmole of 2 (95.8 GLC area % pure) 1.411 mmole of 3 (99.8 GLC area % pure) and 0.493 mmole of 4 (∿94 GLC area pure).

3,6-Dichloro-2-methylthiopyridine-2,6-^{14}C (5)

2,3,6-Trichloropyridine-2,6-^{14}C (257.3 mg, 1.411 mmole) and DMF (2 ml) were added to a 100-ml round-bottomed flask. The solution was cooled to 5°C under N_2 and 1.41 mmole of $NaSCH_3$ in 3.36 ml of DMF added dropwise over a 5 min period with stirring. The resultant mixture was stirred 0.5 hr at 5°C and 0.5 hr at 24°C. It was treated with 50 ml of H_2O and extracted continuously with 20 ml of n-pentane over an 11 hr period.

The solvent was removed in vacuo affording 284.8 mg of yellow oil containing by glc 95:7 area % 5 and 4.0 area % 2,6-bis-methylthiopyridine-2,6-^{14}C (Rt=10.4 min).

3,6-Dichloro-2-methylsulfonylpyridine-2,6-^{14}C (6)

The 50-ml round-bottomed flask containing 5 (∿1.41 mmole) was equipped with a stirring bar and the tracer washed with 2 x 1 ml of H_2O to remove trace DMF present. The tracer was mixed with 2 ml of H_2O and 0.12 ml of conc. HCl (37.9%, 1.191 g/ml, 1.48 mmole) and Roman Cleanser bleach (10.0 ml, 5.25% NaOCl, 7.6 mmole) added dropwise over 15 min. The mixture was stirred for 1.0 hr, treated with 5 ml of CH_2Cl_2, and stirring continued for 0.5 hr.

The mixture was treated with $Na_2S_2O_5$ and the CH_2Cl_2 layer transferred to a column containing 100 g of Brinkman Silica

Gel G60. The product was chromatographed with 1:1 (v/v) n-hexane:ethyl acetate to afford 302.8 mg of 3,6-dichloro-2-methylsulfonylpyridine-2,6-^{14}C as a white solid. The tracer was 90.4 GLC area % pure and 97% radiochemically pure (5 x 20 cm Merck Silica Gel 60 F 254 plate, 1:1 (v/v) n-hexane:EtOAc).

3,6-Dichloropicolinonitrile-2,6-^{14}C (7)

3,6-Dichloro-2-methylsulfonylpyridine-2,6-^{14}C (~1.21 mmole), DMF (1.0 ml), and sodium cyanide (72.0 mg) were added to a 50-ml pear-shaped flask equipped with a stirring bar and the flask stoppered. The mixture was stirred at ca 24°C for 5.5 hr. Additional 16.4 mg and 20.6 mg portions of NaCN were added after 3.0 hr and 4.0 hr of stirring, respectively. The mixture was diluted with 10 ml of H_2O, stirred for 15 min in an ice bath, and filtered through a coarse fritted glass filter. The precipitate was washed with 3 x 1 ml of H_2O, dissolved in 2 ml of CH_2Cl_2, and the resultant solution filtered through layers of Na_2SO_4 and $MgSO_4$ respectively into a tared 50-ml round-bottomed flask. The respective filters were rinsed with 7 x 2 ml of CH_2Cl_2 and the final filtrate analyzed by glc to contain 98.3 area % 7.

The solvent was removed in vacuo to afford 199.7 mg (1.1347 mmole at 98.3 area % purity, 93.8% yield) of 3,6-dichloropicolinonitrile-2,6-^{14}C as a white solid.

3,6-Dichloropicolinic Acid-2,6-^{14}C

To the 50-ml round-bottomed flask containing 7 was added 2.0 ml of 27.5N H_2SO_4 solution. The flask was purged with N_2, equipped with a stirring bar and condenser, and heated at 130-135°C for 1.5 hr under a N_2 atmosphere. It was cooled to 5°C and 11.0 ml of 5.0N NaOH slowly added causing precipitation. The mixture was treated with 299.4 mg (3.56 mmole) of $NaHCO_3$, stirred 0.75 hr, and extracted with 5 x 3 ml of CH_2Cl_2. The

aqueous layer was filtered through a pipet containing a glass wool plug into a 100-ml round-bottomed flask to remove trace suspended solids and the filtrate acidified with 5 ml of 1.00N HCl. The resultant solution was extracted with 7 x 2 ml of CH_2Cl_2 and each extract passed through layers of Na_2SO_4 and $MgSO_4$ into a tared round-bottomed flask. The solvent was removed in vacuo affording 167.6 mg (0.8729 mmole, 76.9% yield) of 3,6-dichloropicolinic acid-2,6-^{14}C as a white crystalline solid.

The tracer was transferred to a 50-ml volumetric flask containing 169.0 mg (0.8802 mmole) of unlabeled 99.3% pure 3,6-dichloropicolinic acid and the flask filled to volume with benzene (Solution I). A 0.50 ml aliquot of Solution I was diluted to 10 ml (Solution II). A 1.00 ml aliquot of Solution II was diluted to 100 ml (Solution III).

The solutions were analyzed as described below to afford 20.4 mCi of 99% radiochemically pure 3,6-dichloropicolinic acid-2,6-^{14}C with a specific activity of 11.64 mCi/mmole.

RADIOMETRIC DETERMINATION

The radioactivity was determined in a Packard Tri-Carb Liquid Scintillation Spectrometer using New England Nuclear Aquasol universal liquid scintillation cocktail. Triplicate assays of Solution III were taken.

The radiochemical purity was determined by spotting three 5 x 20 cm Merck silica gel F-254 plates with 0.5 µl aliquots of Solution I along with a standard sample of the acid. The plates were developed in the solvent systems listed below:

Plate	Solvent System	Ratio (v/v)	R_f Value
1	CH_2Cl_2:EtOAc:HCO_2H	25:18:7	0.54
2	$CHCl_3$:EtOAc:HCO_2H	25:18:7	0.40
3	C_6H_6:EtOAc:HCO_2H	20:23:7	0.67

The plates were subsequently scanned using a Vangruard radio-scanner connected to a Hewlett Packard 5830A integrator but no impurities were detected.

The plates were scraped in 5 mm sections and the sections counted. Histogram analyses of the data afforded product of 99.2% radiochemical purity.

Solution III was analyzed by reverse phase HPLC: Waters RCM 100 column, 1.5 ml/min, 3 min at 100% H_2O (1% HOAc), linear program from 0-100% MeOH (1% HOAc) over 30 min, 2 min at 100% MeOH. Thirty-five 1 ml fractions were collected, counted, and an HPLC histogram obtained on the data affording product of 98.9% radiochemical purity with the 1% impurity at 35 min very likely due to an artifact.

ACKNOWLEDGEMENT

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REFERENCES

1. Muelder, W. W. and Wass, M. N. - Agricultural and Food Chemistry 15:508 (1967).

2. Meihle, R. W. and Williams, E. A. - Nature, 210:523 (1966).

3. McKendry, L. H. and Muelder, W. W. - J. Labelled Compounds and Radiopharmaceuticals, XV:87 (1978).

4. McKendry, L. H. Ibid XVIII:629 (1981).